"In Silico Drug Discovery and Development of Existing Drugs and Molecules for Their Novel Pharmacological Activities by using Computer Aided Repurposing Approaches"

A SYNOPSIS

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By

Mr. PravinShridharrao Deshmukh

(M. Pharm.)

Under the supervision of

Dr.S. R. Butle,

Assistant Professor,

School of Pharmacy,

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY,

NANDED-431 606

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1. AIM & OBJECTIVES:

The aim of the present study is to repurpose the existing drugs using Computer Aids.

OBJECTIVES:

The present study is designed with the following objectives:

Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, repurposing of 'old' drugs to treat both common and rare diseases is increasingly becoming an attractive proposition because it involves the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines. Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges that need to be addressed. In this Review, we present approaches used for drug repurposing (also known as drug repositioning), discuss the challenges faced by the repurposing community and recommend innovative ways by which these challenges could be addressed to help realize the full potential of drug repurposing.

Drug repurposing (DR) (also known as Drug Repositioning) is a process of identifying new therapeutic uses(s) for old/available drugs. It is an effective strategy in discovering or developing drug molecules with new pharmacological/ therapeutic indications. In recent years, many pharmaceutical companies are developing new drugs with the discovery of novel biological targets by applying the drug repurposing strategy in drug discovery and development program. This strategy is highly efficient, time saving, low cost and minimum risk of failure. It maximizes the therapeutic value of a drug and consequently increases the success rate. Thus, drug repurposing is an effective alternative approach to traditional drug discovery process. Finding new molecular entities (NME) by traditional or de novo approach of drug discovery is a lengthy, time consuming and expensive venture. Drug repurposing utilizes the combined efforts of activity-based or experimental and in silico-based or computational approaches to develop/identify the new uses of drug molecules on a rational basis. Ti is therefore, believed to be an emerging strategy where existing medicines, having already been tested safe in humans, are redirected based on a valid target molecule to combat particularly, rare, difficult-to-treat diseases and neglected diseases,

Drug repurposing involves exploring new medical uses for existing drugs, including approved, discontinued, shelved and investigational therapeutics. As the new indication is built on already available safety, pharmacokinetic and manufacturing data, drug repurposing represents an expedited way to develop innovative medications, and has found especial interest in the fields of rare and neglected conditions. It is estimated that about one third of recent approvals correspond to repurposing examples, and different public initiatives have been launched to foster the exploration of repurposing opportunities.

Keeping in view the above challenges of discovering new drugs and their urgent need for treating many untreated, life threatening diseases, in present work we aim to discover and explore the novel beneficial therapeutic effects of already existing drugs or molecules. The biological activity spectrum of already existing drugs/molecules will be predicted by using suitable softwares. The beneficial pharmacological activities of the selected drugs/molecules will be further explored by carrying out molecular docking studies, molecular mechanics/molecular dynamics studies (MD simulations), MMGBSA studies and De Novo designing. After successful In Silico evaluation of novel beneficial pharmacological activities of the selected drugs/molecules amongst existing drugs/molecules, their In-Vitro and In-Vivo studies will be carried out in order to confirm the potency and efficacy of the existing drugs for the newly discovered pharmacological activity.

2. INTRODUCTION:

Over the last few decades, computer-aided drug design has emerged as a powerful technique playing a crucial role in the development of new drug molecules. Structure-based drug design and ligand-based drug design are two methods commonly used in computer-aided drug design. In this article, we discuss the theory behind both methods, as well as their successful applications and limitations. To accomplish this, we reviewed structure based and ligand based virtual screening processes. Molecular dynamics simulation, which has become one of the most influential tools for prediction of the conformation of small molecules and changes in their conformation within the biological target, has also been taken into account. Finally, we discuss the principles and concepts of molecular docking, pharmacophores and other methods used in computer-aided drug design.

Role of computer-aided drug design in modern drug discovery:

Drug discovery utilizes chemical biology and computational drug design approaches for the efficient identification and optimization of lead compounds. Chemical biology is mostly involved in the elucidation of the biological function of a target and the mechanism of action of a chemical modulator. On the other hand, computer-aided drug design makes use of the structural knowledge of either the target (structure-based) or known ligands with bioactivity (ligand-based) to facilitate the determination of promising candidate drugs. Various virtual screening techniques are now being used by both pharmaceutical companies and academic research groups to reduce the cost and time required for the discovery of a potent drug. Despite the rapid advances in these methods, continuous improvements are critical for future drug discovery tools. Advantages presented by structure-based and ligand-based drug design suggest that their complementary use, as well as their integration with experimental routines, has a powerful impact on rational drug design. In this article, we give an overview of the current computational drug design and their application in integrated rational drug development to aid in the progress of drug discovery research.

The use of rational drug design, as applied in CADD, provides a knowledge-driven approach that can yield valuable information about the interaction pattern between protein and ligand (complex), as well as the binding affinity. Furthermore, the availability of supercomputers, parallel processing, and advanced software have greatly facilitated the rate of lead identification in pharmaceutical research.

In general, modelling approaches are categorized into structure-based and ligand-based methods .The structure-based approach consists of using the 3D structure of the target (enzyme/receptor) for the generation or screening of potential ligands (modulators), followed by synthesis, biological testing, and optimization. In contrast, ligand-based approach consists of subjecting a collection of molecules with diverse structures and known potency to computational modelling methods to develop theoretical predictive models. These models are then used for structural optimization to enhance potency and for identification of new chemical entities through virtual screening of a large chemical database. Over the decades, these two types of CADD approaches continued to improve and evolve separately. However, combining different structure-based and ligand-based design strategies in the drug discovery

effort have been established to be more effective than any single approach since both methods are able to complement their strengths and weaknesses.

Discoveries about the molecular basis of disease provide unprecedented opportunities to translate research findings into new medicines. However, developing a brand-new drug takes an enormous amount of time, money and effort, mainly due to bottlenecks in the therapeutic development process. Delays and barriers mean that translation of a promising molecule into an approved drug often takes more than 14 years. It is crucial to advance strategies to reduce this time frame, decrease costs and improve success rates.

Drug repurposing is one such strategy. Many agents approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. Because repurposing builds upon previous research and development efforts, new candidate therapies could be ready for clinical trials quickly, speeding their review by the Food and Drug Administration and, if approved, their integration into health care.

Drug repositioning is a promising field in drug discovery that identifies new therapeutic opportunities for existing drugs. In order to circumvent some of the most expensive drug discovery processes, companies pursue this strategy to increase their productivity (new drugs to market) by reducing the discovery and development timeline. This decreases the overall cost of bringing the drug to market because the safety and pharmacokinetic profiles of the repositioned candidates are already established.

The term “drug repositioning” has been used interchangeably with “drug repurposing” or “drug profiling.” All these expressions are relatively synonymous for describing the process that seeks to discover new applications for an existing drug that were not previously referenced and not currently prescribed or investigated for consistency; this review will refer to all research that explores the multiple therapeutic applications of drugs as drug repositioning.

Benefits of drug repurposing:

Drug repurposing has various benefits as compared to conventional procedures to drug discovery. In comparison to conventional drug discovery systems, there is a very significant decrease in the time period exhausted in research and development. To develop a

new drug by conventional procedure, there is no requirement of the initial 6–9 years for a repositioned drug; rather it gets in straightaway to testing and trials phase. Therefore it is decreasing the whole danger, time period, and expenditure of development. The de novo drug discovery is used for searching and designing novel molecular entities with better pharmacokinetics and pharmacodynamic response. This involves different stages, such as discovery design of drug candidates, preclinical and safety assessment, clinical trials, review and approval, and marketing and post approval safety observation. But there are only four phases in the case of drug repurposing, it consists of compound determination, compound acquisition, development, and safety observation after released to the market.

In the case of drug repurposing, a lot of preclinical and clinical knowledge about the candidate drug exists as the drug has already passed through these stages. Drug repurposing suits well for the quickly nascent and re-emerging infectious diseases for which no current therapeutics is available.

3. BACKGROUND:

Clinical trials on combination of repurposeddrugs and anti cancertherapies:

The way of drug repurposing studies:

Drug repositioning opportunities evolve from observations, discussions, and other collaborations, including the purposeful development of platforms for drug identification, which identify the potential targets and allow the accessing of compounds. Drug repurposing candidates can be obtained from drugs in clinical development that have failed to demonstrate efficacy for a particular indication during Phase II or III trials but have no major safety concerns and drugs that have been discontinued for commercial reasons and drugs patents are close to expiry in market, and from nonreleased drug candidates. Three main approaches based on computational, biological experimental, and mixed are generally used for drug repurposing studies. Several strategies involved the drug repurposing studies that include various in silico methods, genomic, high-throughput screening technologies, and literature mining. These screening methods also provide opportunities for the exploitation of the open-source model. DrugBank, the Potential Drug Target Database, Therapeutic Target Database, and Super Target represents the open sources that provide targets and drugs, including protein and active-site structures, association with related diseases, biological functions, and signaling pathways. Compound-specific databases are provided by PubChem,

ChEMBL, and ChemSpider, the US FDA's Electronic Orange Book's Discontinued Drug Products List, and ID (Investigational Drug) Map .

DNA Methyltransferase Inhibitors for Cancer Therapy:

Drug Repurposing:

Drug repositioning or drug repurposing is an approach to accelerate the drug discovery process through the identification of a novel clinical use for an existing drug approved for a different indication. The increased success and applications of drug repurposing can be considered as one of the consequences of polypharmacology and it represents a manifestation of the shift from a single to multitarget paradigm in drug discovery.Dueñas-González et al. have commented in detail on the important role of drug repurposing in cancer therapy . Classical examples of drug repurposing in epigenetic compounds targeting DNMTs are the antihypertensive drug hydralazine or the local anaesthetic procainamide (*vide supra*). As reviewed above, procainamide has been a recent subject of optimization programs.

As part of an effort to identify approved drugs with potential for epigenetic therapeutic applications, Mendez-Lucio et al. implemented a computer-guided drug repurposing approach.In that work, a public database of 1,582 approved drugs was subject to a systematic and fast computational search using as a reference molecule NSC14778 , a DNMTi previously identified from virtual screening. The computational search was conducted using 3D similarity searching based on the principles of the molecular similarity that states that similar structures will have similar activity. Among the ten most similar compounds to the reference structure was olsalazine which is an anti-inflammatory drug used in the treatment of inflammatory bowel disease and ulcerative colitis. It was approved by the FDA in 1990. In order to examine the ability of olsalazine to inhibit DNMT activity, a novel DNA methylation reprogramming system that operates in the context of living cells [88] was used. The cell-based screen used in that work is highly tractable, internally controlled and well-suited for a drug repurposing strategy in epigenetics. The authors concluded that olsalazine very closely mimics the action of decitabine with minimal cytotoxicity at the concentrations tested.

The success story of drug repurposing in breast cancer:

Breast cancer is the most common type and the second leading cause of cancer-related deaths in women. As one of the deadliest cancers, treating breast cancer requires the development of efficacious drugs and improved therapeutic strategies. However, the development of new drugs is extremely time-consuming and costly. Thus, identifying new uses of existing nononcology or oncology drugs in treating breast cancer is becoming an important step toward developing better treatment strategies and improving overall outcomes. In this chapter, we discuss some of the successful cases of drugs that were repositioned and highlight the scope of new approaches and novel candidates that are being currently studied.

DNA Methyltransferase Inhibitors for Cancer Therapy:

DNA methyltransferases (DNMTs) are promising epigenetic targets for the development of novel anticancer drugs and other diseases. 5-Azacytidine and decitabine are DNMT inhibitors (DNMTi) approved by the Food and Drug Administration of the United States for the treatment of myelodysplastic syndromes. These two drugs have demonstrated significant, although usually transient, improvement in patient survival. The promising clinical success and limitations of these approved drugs have prompted the search for novel agents targeting DNMTs using a blend of complementary methods including chemical synthesis, rational search in natural sources and food components, and high-throughput screening. This chapter discusses the therapeutic significance of DNMTs in cancer and successful applications of DNMTi in the clinic. We also present advances on experimental assays to screen compound collections and the current status of DNMTi development. Additionally, we elaborate on data sources and recent applications of chemo informatics and molecular modeling that exemplify the significance of *ChemEpinformatics* in translational epigenetics.

Computational approaches are useful tools to interpret and guide experiments to expedite the antibiotic drug design process. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) are the two general types of computer-aided drug design (CADD) approaches in existence. SBDD methods analyze macromolecular target 3-dimensional structural information, typically of proteins or RNA, to identify key sites and interactions that are important for their respective biological functions. Such information can then be utilized to design antibiotic drugs that can compete with essential interactions involving the target and thus interrupt the biological pathways essential for survival of the microorganism(s). LBDD

methods focus on known antibiotic ligands for a target to establish a relationship between their physiochemical properties and antibiotic activities, referred to as a structure-activity relationship (SAR), information that can be used for optimization of known drugs or guide the design of new drugs with improved activity. In this chapter, standard CADD protocols for both SBDD and LBDD will be presented with a special focus on methodologies and targets routinely studied in our laboratory for antibiotic drug discoveries.

Literature Review:

DiMasi et al. 2003; Song et al. 2009:

Bringing a new drug into the market is a costly process in terms of money, manpower, and time. Drug discovery and development takes an average of 10–15 years with an approximate cost of US$800 million to US$1.8 billion

Jhoti et al. 2013; Lavecchia and Di Giovanni 2013 :

Innovations in combinatorial chemistry that led to the increase of compound databases covering large chemical spaces aided in the expansion of drug discovery and the development of high-throughput screening (HTS).

Paul et al. 2010:

Despite this, the number of new molecular entities (NMEs) successfully launched into the market continued to decrease over the last several years

Jhoti et al. 2013; Lavecchia and Di Giovanni 2013: Innovations in combinatorial chemistry that led to the increase of compound databases covering large chemical spaces aided in the expansion of drug discovery and the development of high-throughput screening (HTS)

Shoichet et al. 2002; Reynolds 2014;

Rodrigues and Schneider 2014To this end, employment of computer-aided drug discovery (CADD) techniques by top pharmaceutical companies and other research groups became essential for the preliminary stage of drug discovery to expedite the drug development process in a more cost-efficient way and to minimize failures in the final stage. Recent successes involving rational drug design have been reported elsewhere.

Macarron et al. 2011; Lionta et al. 2014 :

While HTS continues to be a big part of the drug discovery process in the pharmaceutical industry due to its high success rate, lack of primary understanding of the molecular mechanism behind the activity of the identified hits can hamper the search of promising candidates

Anderson 2003 :

The current scenario of the drug discovery process involves several disciplines such as chemical and structural biology, computational chemistry, organic synthesis, and pharmacology. Accordingly, it is comprised of several stages: Target *identification* involves the discovery and isolation of individual targets to investigate their functions and association with a specific disease

Chen and Chen 2008 :

(b) *Target validation* is the stage where the drug target is linked to the disease of interest, as well as their capacity to regulate biological functions in the body after binding to a partner molecule. Numerous studies are performed to ascertain that the target macromolecule is linked to the diseased state

Kalyaanamoorthy and Chen 2011:

(c) *Lead identification* entails the discovery of a synthetic chemical that shows a degree of potency and specificity against a biological target and is assumed to have the makings of a drug that can cure the intended disease

Andricopulo et al. 2009:

(d) *Lead optimization* covers the improvement of potency and other significant properties through iterative cycles of evaluation of the lead compound(s) and their analogs. Thus, both in vitro and in vivo experiments are conducted to prioritize and select candidates with optimum potential for development as a safe and efficient drug. Moreover, structure–activity relationships (SARs) are developed to determine pertinent pharmacokinetic and pharmacodynamic properties that can be applied to analogs that will be synthesized for evaluation

Cavagnaro 2002; Silverman 2004:

(e) *Preclinical stage* involves drug synthesis and formulation research, in vivo animal studies for potency and toxicity, and characterization of mechanistic toxicity

Silverman 2004:

(f) *Clinical trials* include three phases that investigate safety, adverse side-effects, dosage, efficacy, and pharmacokinetic and pharmacological properties of the candidate drug on human volunteers

4. RATIONALES OF STUDY:

Discovery and development of a new drug is generally known as a very complex process which takes a lot of time and resources. So now a day's computer aided drug design approaches are used very widely to increase the efficiency of the drug discovery and development course. Various approaches of CADD are evaluated as promising techniques according to their need, in between all these structure-based drug design and ligand-based drug design approaches are known as very efficient and powerful techniques in drug discovery and development. These both methods can be applied with molecular docking to virtual screening for lead identification and optimization. In the recent times computational tools are widely used in pharmaceutical industries and research areas to improve effectiveness and efficacy of drug discovery and development pipeline. In this article we give an overview of computational approaches, which is inventive process of finding novel leads and aid in the process of drug discovery and development research.

Molecular modeling and computational chemistry are assuming an increasingly important role in understanding the basis of drug-receptor interactions and assisting the medicinal chemist in the design of new therapeutic agents.

The addition of computer-aided drug design (CADD) technologies to the research and drug discovery approaches could lead to a reduction of up to 50% in the cost of drug design. Designing a drug is the process of finding or creating a molecule which has a specific activity on a biological organism. Development and drug discovery is a time-consuming, expensive, and interdisciplinary process whereas scientific advancements during the past two decades have altered the way pharmaceutical research produces new bioactive molecules. Advances in computational techniques and hardware solutions have enabled *in silico* methods to speed up lead optimization and identification. We will review current topics in computer-aided molecular design underscoring some of the most recent approaches and interdisciplinary processes. We will discuss some of the most efficient pathways and design.

Repurposing has the objective of targeting existing drugs and failed, abandoned, or

yet-to-be-pursued clinical candidates to new disease areas. The open-source model permits for the sharing of data, resources, compounds, clinical molecules, small libraries, and screening platforms to cost-effectively advance old drugs and/or candidates into clinical re-development. Clearly, at the core of drug-repurposing activities is collaboration, in many cases progressing beyond the open sharing of resources, technology, and intellectual property, to the sharing of facilities and joint program development to foster drug-repurposing human-capacity development. A variety of initiatives under way for drug repurposing, including those targeting rare and neglected diseases, are discussed in this review and provide insight into the stakeholders engaged in drug-repurposing discovery, the models of collaboration used, the intellectual property-management policies crafted, and human capacity developed. In the case of neglected tropical diseases, it is suggested that the development of human capital be a central aspect of drug-repurposing programs. Open-source models can support human-capital development through collaborative data generation, open compound access, open and collaborative screening, preclinical and possibly clinical studies. Given the urgency of drug development for neglected tropical diseases, the review suggests elements from current repurposing programs be extended to the neglected tropical diseases arena

5. PLAN OF WORK

5.1 Literature review

5.2 Selection of Drugs/molecules for repurposing

5.3 To study the biological activity spectrum, drug likeness and ADMET of selected drugs/molecules by using In Silico approaches

5.4 To explore the novel pharmacological activities by using In Silico approaches like molecular docking, molecular mechanics, molecular dynamics, MMGBSA, De Novo designing etc.

5.5 To carry out the In-Vitro and In-Vivo studies of successfully repurposed drugs/molecules for their novel pharmacological activities.

6. DURATION OF WORK:

Sr.	WORK	PERIOD
1	Literature review	6 Months
2	Selection of Drugs/molecules for repurposing.	3 Months
3	To study the biological activity spectrum, drug likeness and ADMET of selected drugs/molecules by using In Silico approaches.	3 Months
4	To explore the novel pharmacological activities by using In Silico approaches like molecular docking, molecular mechanics, molecular dynamics, MMGBSA, De Novo designing etc.	1year
5	To carry out the In-Vitro and In-Vivo studies of successfully repurposed drugs/molecules for their novel pharmacological activities.	1 year
	Total duration of project	**36 Months**

7. RESEARCHOUTCOME:

Repurposing of the existing drugs using Computer Aided Drug Design is widely used tool for identifying the possible other uses of the drug. The technique saves the time and money which is required for the new drug development.

The repurposing of existing drugs allows the systematic and comprehensive approach for the other possible uses of the drugs other than it was intended for.

Drug repurposing (DR) (also known as Drug Repositioning) is a process of identifying new therapeutic uses(s) for old/available drugs. It is an effective strategy in discovering or developing drug molecules with new pharmacological/ therapeutic indications.

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